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Atty. Docket: UCONEN/207/US

REMARKS

Claims 3-4, 32 and 34 are being cancelled without prejudice to filing in a subsequent application and to save amendment fees in this Response. Claims 1-2 and 6-31 are being amended. Claims 41-44 are being added. The specification is being amended the specification at pages 31, 34, and 36 to correct errors. Applicant notes that claims 33, and 35-40 were previously cancelled without prejudice to filing in a subsequent patent application. Upon entry of this amendment, claims 1-2, 5-31 and 41-44 will be pending in the application.

Patentable Subject Matter

Applicant thanks the Examiner for indicating that claims 1-31 contain patentable subject matter.

Amendment to the Specification

Applicant has amended the specification at pages 31, 34, and 36.

Amended Structure of Compound Number 16

The specification at page 31, TABLE 1, compound number 16 has been amended to correct a clerical error. The as filed structure for compound number 16 illustrates a methyl ester group (Ome) on the C ring, carbon 9 and a hydroxyl group (OH) on the A ring, carbon 1. As amended, the methyl ester group (Ome) is now correctly present on the A ring, carbon 1 and the hydroxyl group (OH) is now correctly present on the C ring, carbon 9.

Applicant notes that the amended structure for compound 16 is supported by the specification as filed at page 11, lines 21-24. The specification as filed also includes data generated through the use of compound 16 having a structure as shown in the amended molecule. For example, Table 2 discloses that compound 16, as correctly represented in the amendment, has specific characteristics with regard to absorbance peak, mol extinction, fluorescence excitation peak, fluorescence emission peak, and Stoke's shift. In addition, Table 3 discloses that compound 16, as correctly represented in the amendment, has specific CB1 and CB2 Ki values.

In summary, the structure for amended compound 16 is supported by the generic description in the specification and by the disclosed data that is inherently associated with the amended structure of compound 16 and by at least page 11, lines 21-24 of the specification as filed. As such, the amended structure of compound 16 adds no new matter and should be entered.

Amendment to Table 2

Applicant has amended Table 2, at page 34, to correct clerical errors that resulted in mismatching experimental data with experimental compounds. Compounds 1 and 8, which inherently have the properties listed in TABLE 2, support this amendment. As such, the amendment to TABLE 2 adds no new matter and should be entered.

Amendment to Table 3

Applicant has amended Table 3, at page 36, to delete the data associated with compound 20.

Amendment to the Claims

Claims 1 and 3 were amended to add the phrase "or a physiologically acceptable salt thereof". This amendment is supported by the as filed specification at page 4, line 11. Claim 3 was amended to recite some of the possible substituents for the Y moiety. This amendment is supported by as filed claim 4.

The Objection to Claims 1-31 as containing non-elected subject matter

The Office communication objects to claims 1-31 as containing non-elected subject matter.

On May 20, 2004 the Office mailed a communication restricting Applicant's claims to one of five asserted inventions. This Office communication identified the asserted inventive groups by reference to both exemplified compounds in Applicant's TABLE 1 and PTO class and subclass. Applicant's elected Group IV (with traverse) in their July 21, 2004 Response for prosecution in this application.

Applicant notes that the restriction itself and the relationship between the exemplified compounds and the PTO class/subclass asserted in the restriction is not clear. For example, Group I was indicated to be:

Claims 1-40, drawn to compounds of formulae I, II, III or IV where compounds are represented by exemplified compounds 1-8 (see table 1 on page 30), pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 549, subclass 286.

Class 549, subclass 286 is indented under, and includes, subclass 285, which is indented under, and includes, subclass 283. Subclass 283 is for compounds "wherein the polycyclo ring system consists of exactly two rings." Subclass 285 is for compounds "wherein an additional chalcogen is bonded directly to the six-membered lactone ring." Subclass 286 is for compounds, with underlining added "wherein a benzene ring and the six-membered lactone ring are both bonded directly to the acyclic carbon." Thus, subclass 286 is for compounds having a benzene ring linked through an acyclic carbon to a specified fused bicyclic ring system. See the compounds exemplified under subclass 286. Subclass 286 does not appear to be relevant to Applicant's compounds 1-8 which do not have the structure required by subclass 286 including the required linking acyclic carbon. Further, the differences between compounds 1-8 as included with Group I and 9-16 as included with elected Group IV are not clear.

Group II was indicated to be:

Claims 1-40, drawn to compounds of formulae I, II, III or IV where compounds are represented by exemplified compounds 20-23 (see table 1 on page 31), pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 544, subclass 147.

Class 544, subclass 147 is indented under the following classes/subclasses: 544/106, 544/98, 544/63, 544/1, 540, 532, 260. Class 544, subclass 147 is directed to compounds having a morpholine ring and additionally a hetero ring that includes a ring oxygen. Class 544, subclass 98, which limits subclass 147, is for compounds "wherein the six-membered hetero ring has oxygen in the 1-position, nitrogen in the 4-position and carbons in the remaining four positions." Compounds 20-23 do have a morpholine

ring, however that ring appears to have the linking nitrogen in the 1 position and the oxygen in the 4 position, which is contrary to subclass 98. Applicant can, at best, speculate that the difference between compounds 20-23 as included with Group II and 9-16 as included with elected Group IV is the heterocyclic ring linked to the R₂ position.

Group III was indicated to be:

Claims 1-40, drawn to compounds of formulae I, II, III or IV where compounds are represented by exemplified compound 49 (see table 1 on page 33), pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 546, subclass 80.

Class 546, subclass 80 is indented under the following classes/subclasses: 546/79, 546/26, 546/1, 260. Class 546, subclass 80 requires a tricyclo ring system having a six membered hetero ring with a nitrogen ring atom and at least one additional ring heteroatom. Compound 49 appears to meet this criterion because X is nitrogen and Z is oxygen.

Group IV was indicated to be:

Claims 1-40, drawn to compounds of formulae I, II, II, or IV where compounds are represented by exemplified compounds 9-16 (see table 1 on page 30), pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 549, subclass 263.

Class 549, subclass 263 is indented under the following classes/subclasses: 549/200, 549/1. Class 549, subclass 263 is defined as, with bracketed text added:

Compounds wherein the [oxygen containing] hetero ring is a lactone, i.e., a cyclic inner ester, wherein -O- is part of the ring, X is chalcogen (i.e., oxygen, sulphur, selenium or tellurium).

In sum, the relevance of Groups I and II is not understood since the exemplified compounds and class/subclass designations do not appear to align. The pending claims have been amended to recite Z is oxygen (thereby falling within the Group IV class 549/ subclass 263 designation) and X is carbon (thereby remaining outside of the

Group III class 546, subclass 80 designation). Applicant believes the amended claims are properly limited under the restriction to Group IV as best understood.

Applicant points out that the amended claims do not have alkyl (C-C) or aryl as a Y moiety possibility. Thus, these claims would appear to be allowable over the prior art for the reasons set out in page 4 of the Office communication.

Applicant also points out that the claims as amended present a neat and logical separation from the claims of divisional applications that will likely be filed.

Claim Rejections Under 35 U.S.C. §112 Second Paragraph

Claims 1-31 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite or failing to particularly point and distinctly claim the subject matter which the Applicant regards as the invention. Specifically, the Office communication stated that:

In claims 1-31, the values of all variables defined as ---comprising--- is indefinite since it is not clear whether these substituents are attached directly or indirectly to the tricyclic ring system. . . .

In claim 1, it is not clear what is being used to excite the cannabinoid compound? Also is this method *in vivo* method or *in vitro* method?

In claims 3, 4 and 20, the values of variables X, Z, R2, R3, R4 and R5 are not defined.

In claim 3, the value of variable Y defined as ---electron rich element--- is indefinite since this element is not defined.

In claim 17, the term ---sample--- is indefinite since its meaning is not clear.

In claims 18 and 19, the term ---interacting is indefinite since its meaning is not clear. Also, which receptor subtype is being interacted?

In claim 20, it is not clear how the fluorescent property is detected.

Claim 1 provides for the use of fluorescent cannabinoid compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Applicant respectfully reminds the Examiner that "[t]he requirement that the claims 'particularly point out and distinctly claim' the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when read in conjunction with the rest of the specification. 'If the

claims read when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." "A claim is not 'indefinite' simply because it is hard to understand when viewed without the benefit of the specification." S3 Inc. v. Nvidia Corp., 259 F.3d 1364, 59 U.S.P.Q.2d 1745 (Fed. Cir. 2001).

Use of Word "Comprising" in Claims 1-31

As suggested by the Examiner, Applicant has amended the claims where appropriate to replace the word "comprising" with "is" or "is selected from". These transitional terms are exemplified in the MPEP (May 2004), Appendix AI, Example 20 and Training Materials For Examining Patent Applications With Respect to 35 USC section 112, First Paragraph - Enablement Chemical/Biotechnical Applications, Examples H and J. As such, any proper rejection of the claims under 35 U.S.C. §112, second paragraph has been obviated.

Claim 1 Clearly Recites Active and Positive Steps

The Office communication asserts claim 1 is unclear since it "does not set forth any steps . . ." Applicant is confused by this assertion since the claims under consideration recite active, positive steps such as "providing," "exciting", and "detecting." As such the claims "set out and circumscribe a particular area with a reasonable degree of precision and particularity," In re Moore, 58 CCPA 1042, 439 F.2d 1232, 169 USPQ 236 (1971); and make it clear what subject matter these claims encompass, In re Hammack, 57 CCPA 1225, 1230, 427 F.2d 1378, 1382, 166 USPQ 204, 208 (1970), as well as making clear the subject matter from which others would be precluded, Id. Applicant's position is also supported by Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) and MPEP §2173.05(q). Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

Claim 1 Is Clear in Light of at Least the Specification and Knowledge in the Art

The Office communication asserts that: "it is not clear what is being used to excite the (fluorescent) cannabinoid compound". Applicant is again confused by this

assertion since fluorescence is specifically defined in the specification as filed and is extremely well known in the sciences generally.

For example, Applicant respectfully directs the Examiner's attention to the specification at page 21, lines 15-18. This paragraph reads: "[u]nless otherwise specifically defined "fluorescence" refers to the emission of, or the property of emitting, electromagnetic radiation by a molecule resulting from and occurring only when that molecule is **excited by the absorption of radiation from some other source**" (emphasis added). In addition, page 24 of the specification clearly discusses technologies¹ which inherently use various specific excitation mechanisms.

Furthermore, Applicant attaches herewith pages 346-7 from Biochemical Calculations (How to Solve Mathematical Problems in General Biochemistry, John Wiley & Sons) (1976) as one reference to the Examiner. The Biochemical Calculations reference discusses fluorescence in at least one specific application. Clearly, based on a reading of the specification and with reference to the knowledge in the art, a proper rejection of claim 1, based on the above Office communication statement, cannot be maintained. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

The Office communication questions whether the method of claim 1 is directed to an "in vivo or in vitro method". Applicant notes that the plain language of claim 1 is not limited to either an *in vivo* or *in vitro* method. Applicant notes that at a minimum both *in vitro* and *in vivo* methods are encompassed by claim 1 and as would be evident to one

¹ Some applicable fluorescence technologies useful with the inventive method include, for example, Fluorescence Microscopy, Fluorescence Polarization Spectroscopy, Fluorescence Resonance Energy Transfer Analysis, Flow Cytometry, Fluorescence Photo-Bleach, Immunofluorescence, and Fluorescent Competitive Binding Assay. It should be understood that the present method encompasses use of the inventive compounds in any technology wherein their fluorescent properties are desirable. Thus, the inventive fluorescent cannabinoids can be employed as Fluorescent Molecular Probes, Fluorescent Imaging Agents, Fluorescent Control Standards and Cellular Markers in a broad scope of biomedical research involving cannabinoid receptors. In addition, the fluorescent cannabinoids can be applied in clinical use as Fluorescent Diagnostic Agents to determine therapeutic drug levels and the presence of drugs of abuse in fluids. The fluorescent cannabinoids can also be used as diagnostic agents for determination of white blood cells that have a high concentration of CB2 receptors.

of ordinary skill in the art at the time the invention was made². Clearly, based on a reading of the specification and with reference to the knowledge in the art, a proper rejection of claim 1, based on the above Office communication statement, cannot be maintained. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

Claims 3, 4, and 20 are Clear in Light of at Least the Specification and Knowledge in the Art

The Office communication correctly states that “the values of variables X, Z, R2, R3, R4 and R5 are not defined” in claims 3, 4, and 20. Claim 4 has been canceled. Applicant respectfully points out that the claims 3 and 20 both recite compound structural formulas. Claims 3 and 20 also recite substituent moieties for some positions of these structures. As such, Applicant asserts that claims 3 and 20 are definite and encompass compounds having the recited structure and falling within the plain language of these claims, including those compounds which have ANY substituents for the variables X, Z, R2, R3, R4 and R5. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

Claim 3 is Clear in Light of at Least the Specification and Knowledge in the Art

The Office communication states that the “electron rich element” is “indefinite since this element is not defined”. Applicant respectfully disagrees that the term is indefinite. For example, the specification clearly discloses some electron rich elements at page 3, line 9-10; page 4, line 34; page 8, line 19; page 11 and as filed claims 4, 6, 9-11, 15-16, 20-21, 24-26 and 30-31. However, in order to hasten the prosecution of this particular application, Applicant has amended claim 3 to replace “electron rich element” with O, S, NH, N-alkyl, N-substituted alkyl, N=N, C=C and C≡C. As such, the rejection of claim 3 under 35 U.S.C. §112, second paragraph is been obviated.

² *In Vivo Fluorescence Detection of Ovarian Cancer in the NuTu-19 Epithelial Ovarian Cancer Animal Model Using 5-Aminolevulinic Acid (ALA)* Major A.L.; Rose G.S.; Chapman C.F.; Hiserodt J.C.; Tromberg B.J.; Krasieva T.B.; Tadir Y.; Haller U.; Disaia P.J.; Berns M.W., *Gynecologic Oncology*, July 1997, vol.

Claim 17 is Clear in Light of at Least the Specification and Knowledge in the Art

The Office communication asserts that the term "sample" is "indefinite since its meaning is not clear". Webster's New Collegiate Dictionary, 1974 ed., defines sample as: "a representative part of a single item from a larger whole or group presented for inspection . . .". The McGraw-Hill Dictionary Of Scientific And Technical Terms, 1989 ed., defines sample as: "representative fraction of material tested or analyzed . . ." Further, the concept of samples and sampling is well understood in the scientific arts and is taught to students at grade school levels.

As another example, Applicant directs the Examiner's attention to The Biochemical Calculations, page 347 where it is discussed a sample "**might be** (emphasis added) diluted urine, or serum, or an enzyme mixture containing organic buffers".

These definitions and concepts are further supported by Applicant's specification. For example, reference to test samples in conjunction with the techniques³ disclosed on page 24; and "biopsy samples", page 27, line 25. Clearly one skilled, or even relatively unskilled, in the relevant art would understand the phrase test sample since. Although the term and concept of a sample appears clear, Applicant has amended claim 17 to recite test sample. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

66, no. 1, pp. 122-132(11); Biochemical Calculations (How to Solve Mathematical Problems in General Biochemistry, John Wiley & Sons), pages 346-7 (1976).

³ Fluorescence Microscopy, Fluorescence Polarization Spectroscopy, Fluorescence Resonance Energy Transfer Analysis, Flow Cytometry, Fluorescence Photo-Bleach, Immunofluorescence, and Fluorescent Competitive Binding Assay. It should be understood that the present method encompasses use of the inventive compounds in any technology wherein their fluorescent properties are desirable. Thus, the inventive fluorescent cannabinoids can be employed as Fluorescent Molecular Probes, Fluorescent Imaging Agents, Fluorescent Control Standards and Cellular Markers in a broad scope of biomedical research involving cannabinoid receptors. In addition, the fluorescent cannabinoids can be applied in clinical use as Fluorescent Diagnostic Agents to determine therapeutic drug levels and the presence of drugs of abuse in fluids.

Claims 18 and 19 are Clear in Light of at Least the Specification and Knowledge in the Art

The Office communication states that the term "interacting" is "not clear". Applicant respectfully directs the Examiner's attention to page 25, line 6-8 of the specification, which gives an example of the term "interacting". As illustratively recited by this passage, "[t]he inventive cannabinoid agonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to initiate a physiological or a pharmacological response characteristic of that receptor. One skilled in the relevant art would understand the term "interacting". As such, a proper rejection of claims 18 and 19 based on the above Office communication statement, cannot be maintained. Applicant respectfully traverses this rejection and asserts that it should be withdrawn.

Claim Rejections Under 35 U.S.C. §101

Claim 1 has been rejected under 35 U.S.C. §101 as failing to "set forth any steps involved in the process". The Office communication appears to reference M.P.E.P. § 2173.05(q) ("Attempts to claim a process without setting forth any steps involved in the process" may be rejected properly under "35 U.S.C. 101. In *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967),...") As discussed above, with regard to the 35 U.S.C. §112, second paragraph rejection, the claims under consideration recite active, positive steps such as "providing," "exciting", and "detecting." As such, Applicant respectfully asserts that claim 1 is proper.

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In summary, Applicant has addressed each of the objections and rejections within the present Office Action. It is believed the application now stands in condition for allowance, and prompt favorable action thereon is respectfully solicited.

Respectfully submitted,

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How to Solve Mathematical Problems in General Biochemistry

Second Edition

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aliquots were removed and added to 2.9 ml of 0.1 N NaOH. The concentration of free *p*-nitrophenol was determined by measuring the absorbance at 400 nm against a *p*-nitrophenyl- β -galactoside + buffer + NaOH blank. (a_m of *p*-nitrophenol in 0.1 N NaOH is 18,300.) The cell-free extract contained 5 mg protein/ml. The absorbance of the NaOH solution in a 1 cm cuvette is shown below.

<i>Incubation time (minutes)</i>	$A_{400\text{nm}}$
2	0.09
4	0.18
6	0.27 *

Calculate the specific β -galactosidase activity of the cell-free extract.

Solution

$$v = \Delta A / \text{min} = 0.045/\text{min}$$

$$\Delta A = (a_m)(\Delta c)(l) \quad \text{or} \quad \Delta c = \frac{\Delta A}{(a_m)(l)}$$

$$\Delta c = \frac{0.045}{(18.3 \times 10^3)(1)} = 2.46 \times 10^{-6} M \times \text{min}^{-1}$$

Thus, the concentration of *p*-nitrophenol in the NaOH solution increased at a rate of $2.46 \times 10^{-6} M/\text{min} = 2.46 \times 10^{-5} \mu\text{mole} \times \text{ml}^{-1} \times \text{min}^{-1}$. The volume of the NaOH solution is 3.0 ml. $\therefore (3)(2.46 \times 10^{-5}) = 7.38 \times 10^{-5} \mu\text{mole}$ of *p*-nitrophenol produced/min. The $7.38 \times 10^{-5} \mu\text{mole}$ were produced each minute in 0.1 ml of assay mixture. In the assay mixture:

$$v = 7.38 \times 10^{-2} \mu\text{mole} \times \text{ml}^{-1} \times \text{min}^{-1}$$

The 1.0 ml of assay mixture contained 0.25 ml of cell-free extract. The protein concentration in the assay was:

$$(0.25 \text{ ml}/\text{ml})(5 \text{ mg protein}/\text{ml}) = 1.25 \text{ mg}/\text{ml}$$

$$\therefore \text{S.A.} = \frac{7.38 \times 10^{-2}}{1.25} = \boxed{0.059 \text{ units/mg protein}}$$

Note that by 6 min, $(7.38 \times 10^{-2})(6) = 0.4428 \mu\text{moles}$ of substrate had been utilized. This represents 14.8% of the initial substrate concentration. The fact that the appearance of product is still linear with time indicates that [S] remains $\gg K_m$ and $v = V_{\text{max}}$.

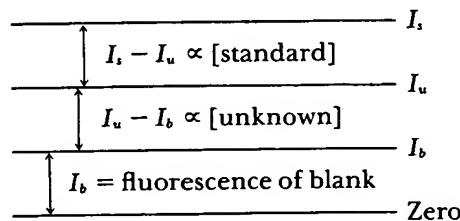
B. FLUOROMETRY

Many compounds absorb light and then immediately reemit some of the energy as light of a longer wavelength. This *fluorescence* phenomenon can be used with an instrument called a fluorometer to measure very low concentrations of certain compounds. A fluorometer differs from a spectrophotometer in that (a) the emitted fluorescence light is observed at 90° to the incident

light and (b) two wavelength selectors are required—one to transmit the desired excitation λ and one to select the desired emission λ . Usually filters (singly or in combination) are used to select the desired wavelengths.

Fluorometry can be extremely selective since only certain wavelengths of light will excite a given compound. Similarly, the fluorescence will occur only at certain wavelengths. In other words, fluorescent compounds have a characteristic excitation spectrum and a characteristic fluorescence spectrum. Two compounds with sufficiently different excitation and/or fluorescence spectra may be determined in the presence of each other in much the same manner as described earlier for spectrophotometry. A compound that does not fluoresce can often be chemically or enzymatically converted to another that does fluoresce.

At low concentrations of a fluorescent compound, the intensity of the fluorescence is directly proportional to concentration. Thus, fluorescence intensity is analogous to absorbance in spectrophotometry, (the linear parameter) not transmission (the logarithmic parameter). The fluorescence emitted by one substance may be absorbed or *quenched* by other substances in the sample. For this reason it is necessary to include an internal ("recovery") standard in each assay. For example, 25 μg of pure compound X might yield a fluorescence intensity of 53 arbitrary units all by itself. However, if 25 μg of pure compound X is added to the sample (which might be diluted urine, or serum, or an enzyme assay mixture containing organic buffers) we may observe an increase of only 29 units above that of the sample itself. Clearly, only $29/53 = 54.7\%$ of the standard's fluorescence is observed under the assay conditions. Thus, under the assay conditions, 25 μg of X is equivalent to 29 units of fluorescence (not 53 units). It is also necessary to subtract from the readings the fluorescence of a blank. The blank should contain the same substances as the sample. For example, if the sample is treated chemically to induce fluorescence, the blank should contain the same chemicals, although added in an order that does not convert the compound being measured to a fluorescent product. The readings can be diagrammed as shown below.



where

I_b = fluorescence of blank

I_u = fluorescence of unknown plus blank

I_s = fluorescence of internal standard plus unknown plus blank

∴ $I_u - I_b$ = fluorescence of unknown under assay conditions

$I_s - I_u$ = fluorescence of standard under assay conditions

and

$$\frac{\text{fluorescence of unknown}}{\text{fluorescence of standard}} = \frac{\text{amount of unknown}}{\text{amount of standard}}$$

or

$$\frac{I_u - I_b}{I_s - I_u} = \frac{\text{amount of unknown}}{\text{amount of standard}}$$

(6)

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